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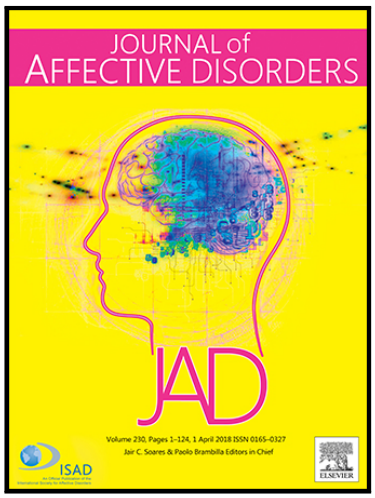

Concordance of Genetic Variation that Increases Risk for Anxiety Disorders and Posttraumatic Stress Disorders and that Influences their underlying Neurocircuitry

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Highlights

- Little work on the concordance of genetic variation between PTSD or anxiety disorders and brain volume has been conducted
- There is evidence for genome wide concordance between genetic risk factors for anxiety disorders and smaller amygdala volume
- A genetic variant that contributes to both reduced putamen volume and PTSD plays a key role in the glutamatergic system
- Larger sample sizes will enhance statistical power in future iterations of this analysis

Concordance of Genetic Variation that Increases Risk for Anxiety Disorders and Posttraumatic Stress Disorders and that Influences their underlying Neurocircuitry

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Abstract

Background: There have been considerable recent advances in understanding the genetic architecture of anxiety disorders and posttraumatic stress disorder (PTSD), as well as the underlying neurocircuitry of these disorders. However, there is little work on the concordance of genetic variations that increase risk for these conditions, and that influence subcortical brain structures. We undertook a genome-wide investigation of the overlap between the genetic influences from single nucleotide polymorphisms (SNPs) on volumes of subcortical brain structures and genetic risk for anxiety disorders and PTSD.

Method: We obtained summary statistics of genome-wide association studies (GWAS) of anxiety disorders (N_{cases}=7016, $N_{controls}$=14745), PTSD (European sample; N_{cases}=2424, $N_{controls}$=7113) and of subcortical brain structures (N=13171). SNP Effect Concordance Analysis (SECA) and Linkage Disequilibrium (LD) Score Regression were used to examine genetic pleiotropy, concordance, and genome-wide correlations respectively. SECAs conditional false discovery was used to identify specific risk variants associated with anxiety disorders or PTSD when conditioning on brain related traits.

Results: For anxiety disorders, we found evidence of significant concordance between increased anxiety risk variants and variants associated with smaller amygdala volume. Further, by conditioning on brain volume GWAS, we identified novel variants that associate with smaller brain volumes and increase risk for disorders: rs56242606 was found to increase risk for anxiety disorders, while two variants (rs6470292 and rs683250) increase risk for PTSD, when conditioning on the GWAS of putamen volume.

Limitations: Despite using the largest available GWAS summary statistics, the analyses were limited by sample size.

Conclusions: These preliminary data indicate that there is genome wide concordance between genetic risk factors for anxiety disorders and those for smaller amygdala volume,

which is consistent with research that supports the involvement of the amygdala in anxiety disorders. It is notable that a genetic variant that contributes to both reduced putamen volume and PTSD plays a key role in the glutamatergic system. Further work with GWAS summary statistics from larger samples, and a more extensive look at the genetics underlying brain circuits, is needed to fully delineate the genetic architecture of these disorders and their underlying neurocircuitry.

Keywords

Anxiety disorders; PTSD; subcortical brain structures; GWAS; genetic concordance

1. Introduction

Anxiety disorders and posttraumatic stress disorder (PTSD) are the most common class of mental disorders (Kessler et al., 2010) and are among the most debilitating (Costello et al., 2005). In the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), a decision was taken to move PTSD into a separate chapter on trauma- and stressor-related disorders, but at the same time it has been emphasized that there are important overlaps in phenomenology and psychobiology across these conditions (Friedman et al., 2011; Hoge et al., 2016). Although many considerations contribute to nosological decisions, ongoing work on the neurogenetics and neurocircuitry of these conditions is needed.

There are significant genetic contributions to the etiology of these disorders with heritability estimates ranging between 10-50% (Hettema et al., 2001; Otowa et al., 2016) and 15-52% (Duncan et al., 2017; Mataix-Cols et al., 2013), respectively. There have been significant recent advances in the understanding of the genetic architecture of anxiety disorders and PTSD. Several genome wide association studies (GWAS) have been undertaken in anxiety disorders; the largest included a total of 18,186 participants from the Anxiety Neurogenetics Study Consortium (ANGST). Taken together these suggest that variants affecting calcium signalling and transmembrane proteins, which are highly expressed in the brain, may play a role (Erhardt et al., 2012; Erhardt et al., 2011; Otowa et al., 2016; Otowa et al., 2009). The largest GWAS of PTSD to date included 20,070 participants from the Psychiatric Genomics Consortium-Posttraumatic Stress Disorder group (PGC-PTSD) found informative polygenic results such as evidence of PTSD heritability (15%) and overlapping genetic risk with other psychiatric disorders (Duncan et al., 2017).

There have also been ongoing advances in understanding the neurocircuitry of anxiety disorders and PTSD. Large collaborations have formed to pool together resources and neuroimaging data for reliable and reproducible findings; these have emphasized structural and functional abnormalities of the amygdala in anxiety disorders (Bruhl et al., 2014; Hattingh et al., 2013; Krain et al., 2008; Massana et al., 2003; Milham et al., 2005), although several other regions have also been implicated in individual studies, including smaller grey matter volumes in the bilateral dorsal and rostral anterior cingulate cortices, bilateral posterior part of the anterior cingulate cortex, and left lenticular nucleus (Radua et al., 2010). Smaller hippocampal volume has been identified in a number of PTSD studies as well as structural anomalies in the dorsal and rostral anterior cingulate cortices, ventromedial prefrontal cortex, amygdala and insula (Gilbertson et al., 2002; Karl et al., 2006; Logue et al., 2018).

Relatively little work to date has, however, focused on examining the genetic overlap between risk for disease and risk for altered brain structure. Exploring genetic correlations and concordance between brain structure and genetic risk for these conditions will provide insight into the pathways affected by the underlying biology of the disorders. The Enhancing Neuroimaging Genetics through Meta-analysis (ENIGMA) consortium performed a GWAS of structural brain MRI scans of 30,717 individuals (Hibar et al., 2015). This study identified novel genetic variants associated with the volumes of the putamen, caudate nuclei, hippocampi as well as the full intracranial volume (Hibar et al., 2015).

ANGST, PGC and ENIGMA freely release summary results of their GWAS, which provides an opportunity to examine the relationship between GWAS data in anxiety disorders and PTSD with the genetic contributions to brain volume. Using SNP Effect Concordance Analysis (SECA)(Nyholt, 2014), we have previously noted evidence of significant positive

concordance between OCD risk variants and variants associated with greater nucleus accumbens ($P=2.0x10^{-4}$) and putamen volumes ($P=8.0x10^{-4}$)(Hibar et al., 2018). Here we expand this analysis to anxiety disorders and PTSD, with the aim of assessing genetic concordance with subcortical volumes and risk variants for these disorders.

2. Methods

2.1 Description of original association studies

We analysed summary statistics from GWASs of the Anxiety NeuroGenetics STudy (ANGST), PGC-PTSD and the ENIGMA Consortium meta-analysis of subcortical brain volumes (Duncan et al., 2017; Hibar et al., 2015; Otowa et al., 2016). The anxiety disorder GWAS was based on case-control samples from 7 European groups contributing to the ANGST Consortium, totalling 7,016 cases and 14,745 controls (Otowa et al., 2016). The ANGST studies included participants with generalised anxiety disorder, panic disorder, social phobia, agoraphobia and specific phobias. Two phenotypic approaches were applied: quantitative phenotypic factor scores and categorical case-control comparisons, resulting in two sets of GWAS results. The PGC-PTSD GWAS was based on case-control samples from 11 contributing groups (totalling 4,522 cases and 15,548 controls of which 87.7% were trauma-exposed) (Duncan et al., 2017). For the purposes of this study, we used the European Ancestry (EA) data, totalling 2,424 cases and 7,113 controls.

The ENIGMA Consortium GWAS of subcortical brain volumes included a meta-analysis of 50 cohorts (Hibar et al., 2015). These data comprised separate GWASs of seven subcortical brain volumes (nucleus accumbens, amygdala, caudate nucleus, hippocampus, globus pallidus, putamen, thalamus), and total intracranial volume. Summary statistics of the GWAS results were available from 13,171 subjects that made up the discovery sample. Brain volume data were extracted following a harmonized protocol that uses validated, robust segmentation algorithms (Fischl et al., 2002) in order to ensure maximum cross-site comparability. All subjects were of European ancestry as verified by MDS analysis and GWAS test statistics were genome-controlled to adjust for spurious inflation factors. The ENIGMA GWAS contain cohorts with healthy controls as well as patients diagnosed with

neuropsychiatric disorders including anxiety, but diagnostic status was controlled for in the analysis (see Hibar *et al*., 2015 Methods, and **Supplementary Table 1** for more details).

2.2 Post-processing of genetic data

After applying quality control and filtering rules to the imputed EA PTSD GWAS data, 13,203,811 SNPs remained (see Duncan et al., 2017 Supplementary Materials for imputation and quality control details). For the anxiety GWAS data, 6,306,613 SNPs remained after filtering (see Otowa et al., 2016 Supplementary Methods for imputation and quality control details). Post-filtering for all 8 brain structures resulted in a final number of 8,398,366 SNPs for the imputed brain volume GWAS data (see Hibar *et al*., 2015 Methods for imputation and quality control details). To statistically compare the EA PTSD and eight brain volume GWASs, we used the 8,156,675 SNPs that passed quality control and filtering rules. To compare the anxiety GWAS with the ENIGMA GWASs, 5,642,909 SNPs were used for the factor score dataset, and 5,661,273 for the case control dataset.

With each dataset, clumping was performed in PLINK (Purcell et al., 2007) to identify an independent SNP from every linkage disequilibrium (LD) block across the genome. This was done separately for each of the eight brain volume GWASs using an 500 Kb window, with SNPs in LD ($r^2 > 0{,}2$), in the European reference samples from the 1000 Genome Project (Phase 1, version 3). The index SNP held the lowest p-value within each LD block, and all other SNPs in the LD block were dropped from the analysis. This resulted in a total of eight independent sets of SNPs, which represented the total variation explained across the genome conditioned on the significance in each brain volume GWAS. The corresponding PTSD and anxiety GWAS test statistic was determined for each independent SNP in the eight sets of SNPs, and used for subsequent analyses.

2.3 Tests of pleiotropy and concordance

SECA (Nyholt, 2014) was used to determine the extent of genetic overlap between PTSD or anxiety and each subcortical volume. A global test of pleiotropy was performed using a binomial test at 12 p-value levels: $P \leq (0.01, 0.05, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1)$. For a given subcortical region and PTSD or anxiety paired set, SNPs were ranked based on their p-value for association with each trait. The total number of SNPs overlapping between the two traits at each p-value threshold was determined and compared to the expected random overlap under the null hypothesis of no pleiotropy, using a binomial test. Each of the 12 p-value levels in the subcortical volume GWAS was compared to all levels of the PTSD and anxiety GWASs (144 comparisons for PTSD and 144 comparisons for anxiety), and the number of comparisons with evidence of overlap was tallied at a nominally significant level of $P \leq 0.05$. To evaluate the global level of pleiotropy we generated 10,000 permuted datasets for a given subcortical region versus PTSD or anxiety comparison and determined if the number of significance thresholds with genetic overlap was significantly greater than chance.

In addition, concordance (the agreement in SNP effect directions across two traits) was estimated using SECA. A significant ($P \leq 0.05$) positive or negative trend in the effect of the overlapping SNPs at each of the 12 p-value thresholds was estimated using a two-sided Fisher's exact test. The direction of effect for each SNP was determined by the sign of the beta value of the SNP regression coefficient from each meta-analysis. In the anxiety disorder and PTSD GWASs, a positive beta value for a SNP was associated with an increased risk of developing anxiety disorders and PTSD (a negative beta value indicates a protective variant). A positive beta value for a SNP in a brain volume GWAS indicates that that SNP is associated with an increase in brain volume (a negative beta value indicates a SNP associated

with a reduction in brain volume). The global level of concordance between a given brain volume phenotype and anxiety disorders or PTSD was estimated by generating 10,000 permuted datasets, repeating the Fisher's exact test procedure, and determining if the number of significant overlapping thresholds was significantly greater than would be expected by chance (see Nyholt *et al*., 2014 for details of the SECA analysis).

A Bonferroni-corrected significance level of P=0.05/2tests*8structures*2disorders=0.00156 was set, based on the number of tests performed for pleiotropy and concordance between anxiety disorders and PTSD and all eight brain structures.

2.4 Conditional false discovery rate to identify risk variants for anxiety disorders and PTSD

We further examined if conditioning the anxiety disorders and PTSD GWAS results on genetic variants that influence subcortical regional volume could improve our ability to identify variants associated with these disorders (Andreassen et al., 2013). For a given subcortical volume phenotype, a subset of SNPs was selected at 14 false discovery rate (FDR) thresholds *q-values* $\leq$ ($1x10^{-5}$, $1x10^{-4}$, $1x10^{-3}$, 0.01, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1). The corresponding p-values for each SNP subset in the PTSD and anxiety GWASs were then observed, and the False Discovery Rate (FDR) method was applied to each subset of p-values in the PTSD and anxiety GWASs (Benjamini and Hochberg, 1995). Significance for individual SNPs was established if the p-value was lower than the significance threshold allowing for a FDR of 5% conditioned on any subset of SNPs from the subcortical volume GWASs. The LD-pruned data are still required for the conditional FDR SNP analysis because the size of an LD block can affect the ranking and re-ranking of SNPs under the conditional models. However, the chosen SNP included in the model is likely a "proxy" for

SNPs in the LD block and should not necessarily be considered the causal variant or even the most significant SNP in terms of its overlap between traits.

We identified variants in LD ($r^2 > 0.5$) within 500kb either side of the significant SNPs using LDLink (https://ldlink.nci.nih.gov/) and SNiPA (https://snipa.helmholtz-muenchen.de/snipa/). Genes that variants were either in, close to, or associated with were annotated using the Gene2Function link on FUMA (http://fuma.ctglab.nl/gene2func/) and Enrichr (http://amp.pharm.mssm.edu/Enrichr/), a pathway analysis software. Further, significant SNPs were annotated using Regulome (http://www.regulomedb.org/index), CADD (https://cadd.gs.washington.edu/), GTeX (https://gtexportal.org/home/) and HUGIn (https://yunliweb.its.unc.edu/hugin/) online software.

2.5 Estimating genetic correlation using LD score regression

We undertook LD score regression (LDSR), which estimates a genetic correlation between two traits based on the GWAS summary statistics of each trait analysed separately (Bulik-Sullivan et al., 2015a; Bulik-Sullivan et al., 2015b). LDSR estimates a genetic correlation with a fitted linear model of Z-scores obtained from the product of significance statistics for each SNP in a given set of GWAS results compared to the level of LD at a given SNP. SNPs in high LD are expected to have high Z-scores in polygenic traits with common genetic overlap (Bulik-Sullivan et al., 2015a; Bulik-Sullivan et al., 2015b). Similar to SECAs concordance test, the genetic correlation from LDSR incorporates the sign of the regression coefficients for each SNP tested in order to determine the direction (positive or negative) of the relation between traits. This amygdala GWAS has previously been shown to have insufficient power for LDSR (Franke et al., 2016). As the amygdala is one of the main structures of interest for anxiety disorders and PTSD, LDSR was not our main analytic choice, and we used it only post-hoc to confirm possible findings with other structures.

Results

3.1 Evidence for pleiotropy between subcortical volume and anxiety disorders and PTSD

Using SECA, we did not find significant evidence of global pleiotropy (regardless of effect direction) for either anxiety disorders or PTSD in any of the subcortical structures studied after correction for multiple comparisons (Table 1).

For anxiety disorders, the evidence of pleiotropy was suggestive between variants affecting amygdala volume and risk using factor score analysis (Table 1, p=0.004), as well as for between variants affecting putamen volume and risk using case-control analysis (Table 1, p=0.01), but this was not significant after correction for multiple testing. For PTSD, suggestive evidence of pleiotropy was observed between variants affecting intracranial volume and risk for PTSD (Table 1, p=0.03), but was not significant after correction for multiple testing.

3.2 Evidence for concordance between the genetics underlying brain volume and anxiety disorders or PTSD

We found significant evidence of concordance (same SNP, direction of effect) between risk variants for anxiety disorders brain volumes. Specifically, we found negative concordance such that variants that increase risk for anxiety disorders, decrease the volume of the amygdala; this was found using both factor score analysis (Table 2, p=0.0001) and case-control analysis (Table 2, p=0.0001). While we observed some evidence for negative concordance in anxiety disorders genetic risk and variants associated with putamen volume when using the factor score dataset (Table 1, p=0.008) and nucleus accumbens volume when using the case-control dataset (Table 2, p=0.002), these findings were not significant after correction for multiple testing.

For PTSD genetic risk, suggestive negative concordance was found for variants associated with amygdala volume (p=0.016), hippocampal volume (p=0.048) and thalamic volume (p=0.01) (Table 2), but these were not significant after correction for multiple testing.

3.3. Genetic variants influencing brain volume regions provide improved ability to detect anxiety risk variants

A conditional false discovery rate (FDR) analysis was performed to separately condition the anxiety disorder and PTSD GWASs on each of the eight brain volume GWASs. Using the factor score dataset for anxiety disorders, we identified three novel variants influencing risk for anxiety disorders when conditioning on the GWAS of amygdala volume (rs77520376, q=0.028), hippocampal volume (rs78587286, q=0.029) and putamen volume (rs56242606, q=0.04) (Table 3a). Furthermore, using the case-control GWAS we found variants influencing anxiety disorders when conditioning on the GWAS of the hippocampal volume (rs28373923, q=0.032), pallidum volume (rs12751736, q=0.041) and thalamic volume (rs2740360, q=0.01) (Table 3b).

For PTSD, two variants were found to significantly influence disorder when conditioned on putamen volume (rs6470292, q=0.048; rs683250, q=0.048) (Table 4).

SNP-based annotation showed there was minimal binding evidence, no associated deleterious effect, and few single tissue eQTLs for the significant variants (Supplementary Material). Expression, gene set and pathway analysis of genes associated with significant variants and variants in LD are available in the Supplementary Materials.

3.4 LD score regression

LDSR findings were consistent with SECA findings for both anxiety disorders and PTSD. A negative genetic correlation between risk for anxiety disorders and putamen volume was

observed (Table 5, p=0.007, r_g=-0.48; Table 6), while a positive genetic correlation was suggested between risk for PTSD and caudate volume (Table 7, p=0.093, r_g=0.35).

4. Discussion

The key findings of this study were 1) a significant concordance between risk variants for anxiety disorders and variants that decrease the volume of the amygdala (p=0.0001) using both factor score and case-control methods for assessing anxiety, and 2) a variant influencing decreased amygdala volume, rs77520376, was significantly associated with anxiety disorders. Although PTSD concordance findings were non-significant after multiple corrections, two variants associated with decreased putamen volume (rs6470292 and rs683250) were also associated with PTSD.

The anxiety disorder findings are consistent with previous work, which has identified decreased grey matter volumes in the amygdala amongst patients with social anxiety disorder (Irle et al., 2010) and panic disorder (Asami et al., 2008; Hayano et al., 2009; Massana et al., 2003). There is, however, also evidence of increased amygdala volume in patients with anxiety disorders (Roth et al., 2018; Schienle et al., 2011; van der Plas et al., 2010). Involvement of the amygdala in anxiety disorders is further supported by functional neuroimaging studies. Hyperactivation of the amygdala in response to various stimuli compared to healthy controls has been observed (Guyer et al., 2008; Hattingh et al., 2013; Monk et al., 2008; van den Heuvel et al., 2005; Wendt et al., 2008), with decreases after successful treatment of specific phobia (Goossens et al., 2007; Ipser and Stein, 2012) and social anxiety disorder (Furmark et al., 2004; Labuschagne et al., 2010).

The variant rs77520376, which is associated with risk for anxiety disorder and decreased amygdala, is located within an intron of the protocadherin-7 (*PCDH7)* gene. PCDH7 plays a role in cell adhesion and calcium ion binding, crucial processes in early brain development

including neural migration, synaptogenesis and axonal growth (Pham et al., 2016). Variants within *PCDH7* have been associated with a number of psychiatric disorders, with trending significant associations with PTSD (Ashley-Koch et al.), bipolar disorder (Le- Niculescu et al., 2009) and epilepsy (Poduri, 2015). Little information is available on this variant, and further attention to its role across a range of psychiatric phenotypes may be useful.

SECA and LD score regression results found marginal significance of putamen volume association with anxiety disorders and PTSD. However, conditioning of anxiety and PTSD GWAS results on genetic variants that influence brain volume showed one variant (rs56242606) significantly associated with decreased putamen volume and anxiety disorders, and two variants (rs6470292, rs683250) significantly associated with decreased putamen volume and PTSD. The variant rs56242606 is located on an intron within the *VWDE* gene, which is in a region of significance recently shown to be associated with anxiety disorders (Purves et al., 2017). Two significant eQTL associations for this variant and *VWDE* were observed (Supplementary Material). The variant, rs683250, associated with decreased putamen volume and PTSD, is found within the *DLG2* gene, which encodes a protein involved in nervous system development, N-methyl-D-aspartate (NMDA) receptor signalling and glutamate receptor binding. NMDA receptors play a central role in modulating fear, anxiety, depression and PTSD (Barkus et al., 2010; Pitman et al., 2012; Yamamoto et al., 2007).

Two additional observations in this study should be considered. First, there were inconsistencies in the results of pleiotropy and concordance for both anxiety disorders and PTSD analyses. Thus, while there was significant concordance between anxiety disorders and amygdala volume, significant pleiotropy was not observed. Whereas pleiotropy indicates that there are variants that affect both phenotype and brain volume, concordance indicates the

specific decrease or increase in a particular subcortical structure. The anxiety and amygdala findings, where concordance is significant and pleiotropy is not, suggest those SNPs that contribute to concordance have predominantly positive or negative effect sizes. Second, there are discrepancies between the findings of factor score analysis and case control analysis; although this is not unexpected given the differences in these approaches, it again suggests that even larger sample sizes would be useful.

Indeed, a number of limitations of this study should be emphasized. First, despite using the largest sample sizes from the brain volume, anxiety and PTSD GWASs to date, false negative findings due to insufficient power cannot be excluded. Second, the relatively small samples do not allow for analyses to be stratified by sex; these may be useful given heritability differences in PTSD in females (29%) compared to males (7%). Third, in theory, the analysis could be biased if overlapping participants were present in the studies contributing to the consortia. LDSR takes possible overlap across studies into account. The relative similarity between the LDSR results and the concordance results therefore suggests that such overlap is likely to be minimal. Fourth, the ENIGMA GWASs of brain volumes contain cohorts with healthy controls as well as patients diagnosed with neuropsychiatric disorders (including anxiety, Alzheimer's disease, attention-deficit/hyperactivity disorder, major depression, bipolar disorder, epilepsy, and schizophrenia), which may bias the interpretation of our findings and how they relate to anxiety disorders and PTSD. However, the brain volume GWASs controlled for diagnostic status, and a direct comparison of the GWAS summary statistics between the full ENIGMA results (including patients) and a subset of ENIGMA results (excluding patients) showed that they were very highly correlated (Pearson's $r > 0.99$) for all brain traits (Hibar et al., 2015). This suggests that the pattern of effects in the brain volume GWAS is not likely driven by disease status. Fifth, the relationship between genetic variants influencing brain volume and neuropsychiatric risk may be influenced by a range of

confounders, including environmental factors such as stress and medication effects, which have effects on brain volume and disease risk independent of genetics (Navari and Dazzan, 2009). Discovering the pathway by which gene variants influencing brain volume also create risk for anxiety disorders and PTSD may be hindered by environmental factors, which might obscure genetic relationships. However, this endeavour to find the genetic overlap between brain volume and disorder risk using the largest datasets to date shows important and promising insights suggesting that our understanding may only be improved when further incorporating environmental influences.

The analyses here complement previous work on OCD, where we found significant positive concordance between OCD risk variants and variants that increase the volume of the nucleus accumbens ($P = 2.0 \times 10^{-4}$) and variants that increase the volume of the putamen ($P = 8.0 \times 10^{-4}$)(Hibar et al., 2018). Investigation of the overlap in genetic variants associated with disorder risk and subcortical neurocircuitry may provide information that could help clarify how anxiety disorders, PTSD, and OCD are related to one another. The findings here arguably support the decision to separate out anxiety disorders and trauma- and stressor-related disorders from obsessive-compulsive related disorders (OCRD) in the fifth edition of the DSM-5 (American Psychiatric Association, 2013; Möller *et al*., 2015). At the same time, we would emphasize that decisions about the DSM-5 meta-structure are complex and a range of other data are needed to inform the debate (Stein, 2008; Stein *et al*., 2011).

This work is the first to show an overlap between genetic risk for anxiety disorders and brain circuitry. The negative genetic concordance between both measures of anxiety and amygdala volume is consistent with a broad range of previous work implicating the amygdala as a critical region for anxiety disorders (Shin and Liberzon, 2009). Emerging collaborations and consortia, such as ENIGMA-PTSD aim to continue to increase sample size, which will

enhance statistical power in future iterations of this analysis. Future work focusing on a range of other methodologies to assess genetic overlap may also be useful, following along the lines of recent work in schizophrenia (Franke et al., 2016; Lee and Huang, 2016). Such studies have used partitioning-based heritability analysis (Yang et al., 2011) and conjunction analysis (Nichols et al., 2005) to identify genetic variants associated with both schizophrenia risk and altered brain volumes, and such approaches, together with analyses such as Mendelian Randomization, may also be useful in future work on anxiety disorders and PTSD, when more powerful GWASs summary statistics are available from larger samples.

Contributors:

All authors approved the final version of the manuscript and participated in the research and article preparation

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Rajendra A. Morey - manuscript review

Paul M. Thompson - manuscript review

Dan J. Stein – conception, design and implementation of study, finalizing manuscript

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Conflict of interest

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Table 1. Pleiotropy results for anxiety disorders or PTSD and subcortical volume overlap (P-value, CI).

Brain volume	Anxiety disorder, Factor score	Anxiety disorder, Case-control	PTSD
Intracranial volume	1 (1-1)	0.159 (0.152-0.167)	0.0333 (0.3-0.037)**
Accumbens	1 (1-1)	1 (1-1)	1 (1-1)
Amygdala	0.0038 (0.00277-0.00521)**	0.297 (0.288-0.306)	1 (1-1)
Caudate	0.0926 (0.0871-0.0984)	0.305 (0.296-0.314)	0.1640 (0.156-0.171)
Hippocampus	1 (1-1)	0.152 (0.145-0.159)	0.3120 (0.303-0.321)
Pallidum	1 (1-1)	1 (1-1)	0.3010 (0.292-0.31)
Putamen	1 (1-1)	0.0101 (0.00832-0.0123)**	1 (1-1)
Thalamus	0.29 (0.281-0.299)	1 (1-1)	1 (1-1)

Bonferroni corrected p-value at 0.05/32 = 0.00156.

**Marginal significance ($p<0.05$)

Table 2. Concordance results for anxiety disorders or PTSD and subcortical volume overlap (P-value, CI, direction of effect).

Brain volume	Anxiety disorder, Factor score	Anxiety disorder, Case-control	PTSD
Intracranial volume	1 (1-1), +	0.257 (0.249-0.266), -	0.0852 (0.0799-0.0908), -
Accumbens	0.164 (0.156-0.171), -	0.0023 ($1.53x10^{-3}$-$3.45x10^{-3}$)**, -	1 (1-1), -
Amygdala	0.0001 ($5.13x10^{-6}$-$5.66x10^{-4}$)***, -	0.0001 ($5.13x10^{-6}$-$5.66x10^{-4}$)***, -	0.0162 (0.0139-0.0189)**, -
Caudate	1 (1-1), +	0.139 (0.132-0.146), -	0.0555 (0.0512-0.0602), +
Hippocampus	1 (1-1), -	0.109 (0.103-0.116), -	0.0479 (0.0439-0.0523)**, -
Pallidum	0.107 (0.102-0.114), +	1 (1-1), -	0.1730 (0.166-0.181), -
Putamen	0.0079 ($6.34x10^{-3}$-$9.83x10^{-3}$)**, -	0.218 (0.21-0.227), -	0.2160 (0.208-0.224), +
Thalamus	0.213 (0.205-0.221), +	0.249 (0.241-0.258), +	0.0101(0.00832-0.0123)**, -

Bonferroni corrected p-value at 0.05/32 = 0.00156.

**Marginal significance (p<0.05)

***Significant (p<0.00156)

Table 3. Significant variants associated with anxiety disorder risk when conditioning on brain volume GWAS. The chromosome (Chr) and base pair (BP) are given in h19b37 coordinates. The Effect in Brain and Effect in AD (anxiety disorders) are both given in terms of the effect allele (EA). The non-effect allele (NEA) is also shown. The allele frequency (Freq) corresponds to the effect allele. Tagging SNP corresponds to the most significant variant in a given LD block (if different from the SNP chosen based on clumping in the brain volume GWAS).

a) Factor score dataset

Brain volume	SNP	Chr	BP	EA	NEA	Freq	Nearest Gene	Distance to Gene	Effect in Brain (SE)	P-value in Brain	Effect in AD (SE)	P-value in AD	q-value
Amygdala	rs77520376	4	30993011	A	G	0.0897	*PCDH7*	Intronic variant	16.172 (4.67)	0.0005369	0.038 (0.009)	$3.21x10^{-5}$	0.0281
Hippocampus	rs78587286	6	14266689	T	C	0.0966	*CD83*	129kb	36.86 (7.88)	$2.87x10^{-6}$	0.0246 (0.008)	0.001954	0.0293
Putamen	rs56242606	7	12421909	T	C	0.9223	*VWDE*	Intronic variant	33.199 (11.91)	0.005299	-0.0417 (0.009)	$6.2x10^{-6}$	0.0402

b) Case control dataset

Brain volume	SNP	Chr	BP	EA	NEA	Freq	Nearest Gene	Distance to Gene	Effect in Brain (SE)	P-value in Brain	Effect in AD (SE)	P-value in AD	q-value
Hippocampus	rs28373923	16	88815473	A	G	0.0753	*PIEZO1*	Intronic variant	-31.994 (12.04)	$7.89x10^{-3}$	0.4193 (0.091)	$4.56x10^{-6}$	0.0317
Pallidum	rs12751736	1	21851462	A	G	0.2889	*ALPL*	Intronic variant	8.669 (2.14)	$5.1x10^{-5}$	0.108 (0.03)	0.0003394	0.0414
Thalamus	rs2740360	17	629309	T	C	0.4398	*FAM57A*	6kb	16.946 (7.01)	$1.57x10^{-2}$	0.1696 (0.033)	$3.81x10^{-7}$	0.0101

Table 4. Significant variants associated with PTSD risk when conditioning on brain volume GWAS. The chromosome (Chr) and base pair (BP) are given in h19b37 coordinates. The Effect in Brain and Effect in post traumatic stress disorder (PTSD) are both given in terms of the effect allele (EA). The non-effect allele (NEA) is also shown. The allele frequency (Freq) corresponds to the effect allele. Tagging SNP corresponds to the most significant variant in a given LD block (if different from the SNP chosen based on clumping in the brain volume GWAS).

Brain volume	SNP	Chr	BP	EA	NEA	Freq	Nearest Gene	Distance to Gene	Effect in Brain (SE)	P-value in Brain	Effect in PTSD (SE)	P-value in PTSD	q-value
Putamen	rs6470292	8	125868043	A	G	0.8155	*MIR4662B*	33kb	-36.2473 (7.71)	$2.55x10^{-6}$	-0.485 (0.048)	0.00184	0.0476
	rs683250	11	83276168	A	G	0.625	*DLG2*	Intronic variant	-33.965 (6.08)	$2.33x10^{-8}$	-0.114 (0.039)	0.003528	0.0476

Table 5. Results of the comparison between each brain volume GWAS from ENIGMA with anxiety disorders GWAS (factor score dataset) using LD score regression

Trait	Brain volume	R_g (SE)	Z-score	P-value
AD	Intracranial volume	0.2672 (0.2158)	1.2378	0.2158
	Accumbens	-0.1296 (0.3151)	-0.4114	0.6808
	Amygdala	NA	NA	NA
	Caudate	-0.1024 (0.1749)	-0.5856	0.5582
	Hippocampus	0.0628 (0.2206)	0.2847	0.7759
	Pallidum	-0.2042 (0.2196)	-0.9298	0.3525
	Putamen	-0.4821 (0.1798)	-2.6814	0.0073**
	Thalamus	0.0311 (0.2126)	0.1463	0.8837

Bonferroni corrected p-value at 0.05/28 = 0.00178

AD, anxiety disorders

**Marginal significance ($p<0.05$)

Table 6. Results of the comparison between each brain volume GWAS from ENIGMA with anxiety disorders GWAS (case-control dataset) using LD score regression

Trait	Brain volume	R_g (SE)	Z-score	P-value
AD	Intracranial volume	0.1565 (0.2191)	0.7141	0.4752
	Accumbens	-0.2242 (0.3128)	-0.7169	0.4734
	Amygdala	NA	NA	NA
	Caudate	-0.0389 (0.155)	-0.2508	0.802
	Hippocampus	-0.1072 (0.2188)	-0.4897	0.6243
	Pallidum	-0.0836 (0.2052)	-0.4076	0.6835
	Putamen	-0.2026 (0.1611)	-1.2573	0.2086
	Thalamus	-0.1075 (0.2288)	-0.4696	0.6386

Bonferroni corrected p-value at 0.05/28 = 0.00178

AD, anxiety disorders

Table 7. Results of the comparison between each brain volume GWAS from ENIGMA with PTSD GWAS (subjects of European ancestry) using LD score regression

Trait	Brain volume	R_g (SE)	Z-score	P-value
PTSD	Intracranial volume	-0.2115 (0.1679)	-1.2599	0.2077
	Accumbens	NA	NA	NA
	Amygdala	NA	NA	NA
	Caudate	0.3512 (0.209)	1.6807	0.0928
	Hippocampus	0.0324 (0.2826)	0.1146	0.9088
	Pallidum	0.2972 (0.2594)	1.1457	0.2519
	Putamen	0.4021 (0.242)	1.6612	0.0967
	Thalamus	-0.318 (0.351)	-0.9058	0.365

Bonferroni corrected p-value at 0.05/24 = 0.002